

stage of the prosecution, the Examiner has complete discretion as to whether to accept this invitation.

#### *Application Status*

Claims 1-16 are pending of which, both of the independent claims (i.e., claims 1 and 11) are amended herein. Paper No. 10, to which this Amendment responds, states that each of the pending claims stand rejected, and that the action is final.

#### *Discussion of the Claim Amendments*

Claim 1 is directed to a method of separating nucleic acid from a test sample. Claim 1 has been amended to make more clear that a direct bond forms between the metal oxide and the nucleic acid in the inventive method. This claim amendment is fully supported by the specification. For example, the specification at page 3, lines 7-25, describes some of the advantages of using metal oxide support materials in the inventive method. This paragraph discloses that metal oxides have a high affinity for nucleic acid sequences, facilitate the collection of even small amounts of nucleic acids, may be employed to separate nucleic acid from a test sample with low organic-solvent concentrations, and can release nucleic acids using elution buffers that are compatible with amplification reactions. Thus, it is clear to those ordinarily skilled in the art that there must be a bond directly between the metal oxide and the nucleic acid because if there was an intervening material one could not discuss the chemical interaction between the nucleic acid and the support particle without identifying the identity or nature of the intervening support material. In this regard, the specification does not discuss coating the particles with any particle substance (e.g., silica). Accordingly, it is clear that the discussion of some of the important advantages of the present inventive method over prior art methods must result from the nature of the bond between the metal oxide and the nucleic acid.

The facts noted above do not mandate that the metal oxide support cannot be partially covered with other substances, unless these substances prevent the formation of metal oxide/nucleic acid bonds.

Claim 11 has also been amended in a manner parallel to claim 1 and is fully supported by the specification for the same reasons.

*Discussion of the Rejections Predicated in Part  
or Entirely on Uematsu et al. (EP 0 757 106)*

The present invention is directed in part to a method of separating a nucleic acid from a test sample comprising the formation of a bond between a metal oxide and a nucleic acid sequence. The Office Action states that each of the pending claims stand rejected entirely, or in part, based on the premise that Uematsu et al. discloses a method of separating a nucleic acid comprising the formation of a metal oxide/nucleic acid bond.

The Office Action states that applicant's arguments in Amendment A are deemed unpersuasive, first, because "Uematsu et al. recites 'separating the magnetic carrier to which the nucleic acid has been bonded from [the test sample]'", and second, because applicant's arguments were allegedly directed to limitations not present in the claims. Each of these reasons for maintaining the claim rejections are addressed separately.

A. Discussion of the Uematsu et al. Reference

Applicant respectfully submits that the Office Action misconstrues the Uematsu et al. reference. A detailed study of the Uematsu et al. reference reveals that it does not disclose or reasonably suggest the use of metal oxide/nucleic acid bonds to separate the nucleic acid from a sample. The Office Action points to page 3, line 46, in support of the position that Uematsu et al. discloses metal oxide/nucleic acid bonding. This sentence recites "a method [including] mixing a nucleic acid-bondable magnetic carrier [with a sample] and eluting the nucleic acid from the magnetic carrier to which the nucleic acid has been bonded." Thus, it appears conceivable that Uematsu et al. describes the formation of a bond between a metal oxide and a nucleic acid. On the other hand, these words are amenable to another interpretation. An equally plausible interpretation is that the term "nucleic acid-bondable magnetic carrier" means a composite particle having two properties (i) that nucleic acids will bond to it, and (ii) that it is magnetic; for example, wherein silica covers a metal oxide core. Applicants respectfully submit that the full text of the Uematsu et al. reference *requires* this latter interpretation.

The sentence at page 3, lines 26-27, of Uematsu separates a discussion of the prior art (to Uematsu et al.) from an allegedly inventive solution to the failings of the prior art. The next sentence (page 3, lines 28-30) identifies the allegedly inventive solution of Uematsu et al. This sentence states that the “nucleic acid-bondable magnetic carrier of the present invention comprises *magnetic silica* particles containing a superparamagnetic metal oxide, wherein the magnetic silica particles have a specific surface of about 100 to 800 m<sup>2</sup>/g.” It is not possible to make “magnetic silica” so it is clear that the “superparamagnetic” metal oxide is present to make the particles magnetic. But is it also there to make the nucleic acid bond to the particle? The answer to this question is not explicitly provided, but it is exceedingly unlikely because it would leave no express or implicit purpose for the silica. Moreover, the specific surface limitation of 100 to 800 m<sup>2</sup>/g given in this sentence appears to refer to the problem of silica coated magnetic particles discussed at page 2, line 39, to page 3, line 10, which are too large or too small. Thus, one must conclude that the nucleic acid-bondable magnetic particles of Uematsu et al. refer to (i) traditional silica coated magnetic particles (ii) of a specific size.

A second reason exists why Uematsu et al. cannot be interpreted to disclose the use of a metal oxide-nucleic acid bond. If the nucleic acid-bondable magnetic carrier of Uematsu et al. does not refer to a silica covered metal oxide, then to what does it refer? The Office Action assumes that Uematsu et al. would be referring to a metal oxide surface. But that teaching is not expressed anywhere in Uematsu et al. In fact, support for the concepts that nucleic acid-metal oxide bonds (i) can be formed and (ii) are suitable for the isolation of nucleic acids occurs only in applicant's disclosure. Of course, applicant's disclosure cannot be properly used to cure the failings of the prior art.

Third, a detailed review of the remainder of the application fails to uncover any other discussion that could conceivably be construed to disclose metal oxide directly bonding to a nucleic acid.

In summary, the best interpretation of Uematsu et al. is that the nucleic acid-bondable magnetic carriers disclosed therein refer to a particle having a magnetic core and a non-metal oxide surface suitable for binding to nucleic acids.

### B. Discussion of the Form of Applicant's Argument

The Office Action states that applicant's arguments in Amendment A were directed to limitations not present in the claims. Applicant is of the opinion that the requirement for direct metal oxide/nucleic acid bonds is readily apparent from the claims, especially in view of the first paragraph of the "Detailed Description of the Invention," which is discussed above. However, the Office Action disagreed. Therefore, applicant has amended the claims, without narrowing them, to make it more clear that the bond is formed between the metal oxide and the nucleic acid (rather than, e.g., through a silica intermediate).

### C. Request for Withdrawal of Rejection

For the reasons discussed in parts A, B, and C, above, applicant respectfully requests that the rejections predicated on the disclosure of Uematsu et al. be withdrawn.

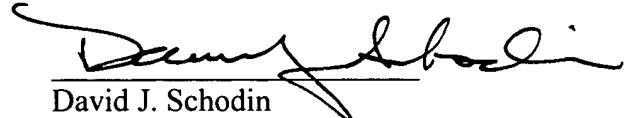
### *Discussion of the Other Claim Rejections*

Parts 5, 6, and 7 of the Office Action state that claims 2-4, 15, and 16 stand rejected over a combination of Uematsu et al. and another reference. None of the other references cure the failing of Uematsu et al. to teach or reasonably suggest the use of a nucleic acid/metal oxide bond to separate a nucleic acid from a sample. Accordingly, applicant respectfully requests that these additional rejections also be withdrawn.

*Conclusion*

In view of the foregoing, applicant respectfully requests the Examiner to indicate the allowability of the subject patent application.

Respectfully submitted,  
G. Gundling

  
David J. Schodin  
Registration No. 41,294  
Agent for Applicants

Dated: May 22, 2001  
ABBOTT LABORATORIES  
D-0377/AP6D-2  
100 Abbott Park Road  
Abbott Park, IL 60064-6050  
Telephone: (847) 937-7022  
Facsimile: (847) 938-2623